(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 127 066
A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 84105521.3

(22) Date of filing: 15.05.84

(51) Int. Cl.³: A 61 K 31/42
C 07 D 263/58

(30) Priority: 20.05.83 US 496755

(43) Date of publication of application:
05.12.84 Bulletin 84/49

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: USV PHARMACEUTICAL CORPORATION
1 Scarsdale Road
Tuckahoe New York(US)

(72) Inventor: Loev, Bernard
42 Penny Lane
Scarsdale New York(US)

(72) Inventor: Brown, Richard E.
16 Ridge Drive
East Hanover New Jersey(US)

(72) Inventor: Huang, Fu-chih
611 Knoll Road
Boonton New Jersey(US)

(72) Inventor: Jones, Howard
79 Briarcliff Woods
Ossining New York(US)

(74) Representative: Patentanwälte Grünecker, Dr. Kinkeldey, Dr. Stockmair, Dr. Schumann, Jakob, Dr. Bezold, Meister, Hilgers, Dr. Meyer-Plath
Maximilianstrasse 58
D-8000 München 22(DE)

(54) Composition for treating asthma.

(57) A new method of treating asthma is provided. The method is the administration of an effective dose of a Benzoxazole-2-carboxylic acid amide.

EP 0 127 066 A2

COMPOSITION FOR TREATING ASTHMA

This invention relates to a new method of treating asthma and, more particularly, to the use of certain heterocyclic amides of use in the treatment of asthma.

Benzoxazole-2-carboxylic acid amides have been described in the literature.

For example, some amides are disclosed in:

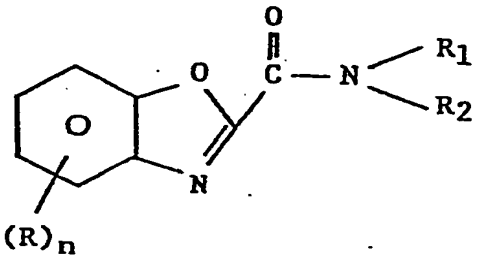
1. Habib and Rees, J. Chem. Soc. 3371-3383 (1960)
2. T. P. Sycheva and M. N. Shchukina, Biol. Aktivn. Soedin., Akad, Navk SSR, 1965, 46-51 CA 64, 6633a (1966)
3. Skravp and Moser, Ber. 55B, 1980-101 (1922) CA 16, 3660 (1922)
4. Farben Fabriken Bayer A.-G. (by Karlfied Dickore, Klaus Sasse, Richard Wegler, and Ludwig Eve).
5. Beilstein Bd. 27, 2nd Revision, p. 379
6. Wright, William Blythe Jr., Brabander, Herbert J. (American Cyanamid Co.) U.S. 3,641,029, Feb. 8, 1972 CA 76 140882b
7. T. P. Sycheva, et al., Kbim. Geterotsikl. Soedin. 1966 (4) 506-10 CA 66 104936p (1967)
8. Farben Fabriken Bayer A.-G. (by Helmuth Hack, et al.) Belgian 659,974, June 16, 1965 CA 66 1977f (1967)
9. Hirono, et al. (Nippon Soda Co., Ltd.) Gen. Offen. 2,350,907 May 2, 1974 CA 81 73416x (1974)

10. Moeller, Hirnich; Gloxhuber Christian (Henkel and Cie. Gm.b.H) Ger. Offen. 2,201,968, Aug. 2, 1973 CA 80 19395f (1974)

11. Karlfried Dickore, et al., Liebigs Ann. Chem 73, 70-87 (1970)

It has now been discovered that certain of the above prior art amides and other new amides are useful in the treatment of asthma.

This invention relates to compositions for the treatment of asthma comprising an effective dose of a benzoxazole-2-carboxylic acid amide of the formula



wherein,

n is 0 - 3,

each R is independently H, halogen, lower alkyl, trihaloalkyl, lower cycloalkyl, hydroxy, lower alkoxy, cyano, carboxyl or carboxy lower alkyl esters, amino, alkylamino, or dialkylamino; and

R_1 and R_2 are independently H, alkyl, aralkyl, haloaralkyl, alkoxyalkyl, alkylcarboxy or where R_1 and R_2 together form a ring group with the nitrogen such as

piperadino, pyrrolidino, or morpholino, etc. and may contain a hetero atom such as oxygen or sulfur. Preferably, the alkyl or the alkyl, alkoxy, aralkyl or haloaralkyl contains one to twelve carbons and it can be branched or straight-chained. Preferably, the lower cycloalkyl contains three to seven carbon atoms.

It is preferred that

n = 0-3,

R is H or chlorine,

R_1 is H, methyl, benzyl or halo-substituted benzyl,

R_2 is H, C_1-C_6 alkyl, or $R_6OC_2H_5$, or $CH_2CO_2R_6$ or CH_2CO_2H wherein R_6 is a C_1-C_4 alkyl or that R_1 and R_2 with the nitrogen form a ring group.

The present heterocyclic amides can be used in the treatment as such or in the form of salts with a wide variety of acids, inorganic and organic, including therapeutically-acceptable acids. The salts with therapeutically-acceptable acids are, of course, useful in the preparation of formulations where water solubility is desired.

The pharmaceutically-acceptable acid addition salts are of particular value in therapy. These include salts of mineral acids such as hydrochloric, hydriodic, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids, as well as salts of organic acids such as tartaric, acetic, citric, malic, benzoic, glycollic, gluconic, gulonic, succinic, aryl-sulfonic, e.g., p-toluenesulfonic acids, and the like. Mineral acid salts are particularly useful for the preparation of the pharmaceutically-acceptable salts, e.g., the hydrochlorides,

by solution in hydrochloric acid and cyrstallization of the hydrochloride salt formed.

The compounds form conjugates with amino acids and the sugar acids. For example, conjugates can be formed with glucuronic acid, e.g., β-D-glucoronic acid, as well as amino acids especially useful in formulation of therapeutic dosage forms.

As therapeutic agents, the present heterocyclic amides act via inhibition of mediator release. These amides are active orally in the passive cutaneous anaphylaxis (PCA) screen; and inhibit histamine release from passively sensitized rat mast cells (RMC).

According to the method of this invention, a therapeutic composition comprising an effective dose of a Benzoxazole-2-carboxylic acid amide of the above formula is administered to a subject suffering from asthma and in need of treatment.

The therapeutic agents used in this invention may be administered in combination with pharmaceutically-acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice. For example, they may be administered in the form of tablets or capsules containing such excipients as starch, milk, sugar, certain types of clay and so forth. They may be administered orally in the form of solutions which may contain coloring and flavoring agents or they may be injected parenterally, that is, intramuscularly, intravenously or subcutaneously. For parenteral administration, they may be used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic.

The physician will determine the dosage of the present therapeutic agents which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary with the particular patient under treatment. He will generally wish to initiate treatment with small dosages substantially less than the optimum dose of the compound and increase the dosage by small increments until the optimum effect under the circumstances is reached. It will generally be found that when the composition is administered orally, larger quantities of the active agent will be required to produce the same effect as a smaller quantity given parenterally. The compounds are useful in the same manner as other anti-allergy agents and the dosage level is of the same order of magnitude as is generally employed with these other therapeutic agents. The therapeutic dosage will generally be from 10 to 750 milligrams per day and higher although it may be administered in several different dosage units. Tablets containing from 10 to 250 mg. of active agent are particularly useful.

The following example further illustrates the invention.

EXAMPLE 1

N-(Ethoxyethyl)-5-chlorobenzoxazole-2-carboxamide

A mixture of 2-ethoxyethyl-5-chlorobenzoxazol-2-carboxylate (10 g) and 3.5 g of ethoxyethylamine in 10 ml of THF was stirred at room temperature for 2 hours. The precipitated product was filtered and washed well with hexane to give 9 g of product; mp 110-111°C.

EXAMPLE 2

N-(t-Butoxycarbonylmethyl)-5-chloro-benzoxazole-2-carboxamide

A mixture of 13.5 g of 2-ethoxyethyl-5-chloro-benzoxazol-2-carboxylate and 6.6 g of t-butyl glycine ester in 50 ml of THF was heated at 70° for 2 days. After cooling, the precipitated product was filtered and washed with hexane to give 3 g of product; mp 152-154°C.

EXAMPLE 3

N-(Carboxymethyl)-5-chlorobenzoxazole-2-carboxamide

Compound from Example 2 (3 g) in 10 ml of trifluoroacetic acid was kept at room temperature overnight. The solvent was removed and ether was added to give 2.9 g of product; mp 222-224° (dec.).

According to Example 1, the following compounds are similarly prepared.

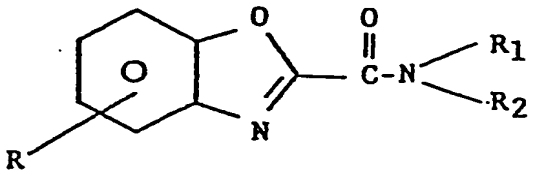
EXAMPLE 4

N-(Ethoxycarbonylmethyl)-5-chlorobenzoxazole-2-carboxamide; mp 121-122°C.

EXAMPLE 5

5-Chloro-benzoxazole-2-carboxylic acid N-β-hydroxyethyl-piperazine amide;
mp 111-112°C.

The compounds in the following table were shown to be useful in the treatment of asthma when screened according to the Rat Passive Cutaneous Anaphylaxis Screen described in I. Mota, Life Sciences, 7 465 (1963) and Z. Ovary, et al., Proceeding Society of Experimental Biology and Medicine, 81, 548 (1952).

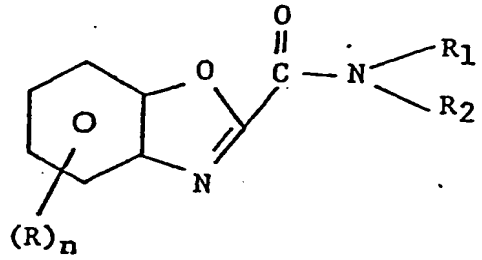


R	R_1	R_2	PCA %I, mg/kg i.p. 10	i.p. 50	P.O. 1	P.O. 10	P.O. 100
H	H	C_6H_5		19			
H	H	CH_3		68			
H	H	tC_4H_9		20			
H	H	H		43			
H	CH_3	CH_3		82			
Cl					24	36	56
Cl	H	$(CH_2)_2OEt$			15	42	52
Cl	H	$CH_2COOC_2H_5$	30				
Cl	H	$CH_2COOtC_4H_9$	29				
Cl	H	CH_2COOH	25				

We claim:

1. A therapeutic composition for the treatment of asthma comprising an effective dose of amide derivatives of benzoxazole-2-carboxylic acid in a pharmaceutical carrier therefor.

2. Composition as in Claim 1 wherein the amide is of the formula



and pharmaceutically-acceptable salts thereof; wherein,

(n) is 0 - 3;

each R is independently H, halo, lower alkyl, trihaloalkyl, cycloalkyl, hydroxy, lower alkoxy, cyano, carboxyl, or carboxy lower alkyl esters, amino, alkylamino, or dialkylamino, and

R_1 and R_2 are independently H, alkyl, aralkyl, aryl, haloaralkyl, alkoxyalkyl, aminoalkyl, or alkylcarboxy and R_1 and R_2 when taken together form a ring group with the nitrogen to which they are attached.

3. Composition as in Claim 2 wherein R_1 and R_2 are independently H or alkyl, alkoxyalkyl, or carboxyalkyl and the alkyl of the alkyl or alkoxy contain one to twelve carbons and the R cycloalkyl contains three to seven carbon atoms.

4. Composition as in Claim 2 or Claim 3 wherein R is H or chlorine.

5. Composition as in any of Claims 2-4 wherein R_1 is H or methyl.

6. Composition as in Claim 2 wherein R_2 is H, alkyl of 1 to 6 carbons, $R_6OC_2H_5$ or $-CH_2CO_2H$, or $CH_2CO_2R_6$ wherein R_6 is an alkyl group of 1 to 4 carbon atoms.

7. Composition as in Claim 2 wherein

R is H or chlorine,

R_1 is H or methyl, and

R_2 is H, alkyl of 1 to 6 carbon atoms, or $R_6OC_2H_5$ or CH_2CO_2H or $CH_2CO_2R_6$ wherein R_6 is an alkyl group of 1 to 3 carbon atoms.

8. Composition as in Claim 2 wherein R is H or chlorine, and R_1 and R_2 together form a ring with the nitrogen to which they are attached.

9. Composition as in Claim 1 or Claim 2 wherein the compound is 5-chloro-benzoxazole-2-carboxylic acid N-β-hydroxyethyl-piperazine amide.

10. Composition as in Claim 1 or Claim 2 wherein the compound is N-(ethoxyethyl)-5-chlorobenzoxazole-2-carboxamide.

11. Composition as in Claim 1 or Claim 2 wherein the compound is N-(ethoxycarbonylmethyl)-5-chlorobenzoxazole-2-carboxamide.

12. Composition as in Claim 1 or Claim 2 wherein the compound is N-(t-butoxycarbonylmethyl)-5-chloro-benzoxazole-2-carboxamide.

13. Composition as in Claim 1 or Claim 2 wherein the compound is N-(carboxymethyl)-5-chlorobenzoxazole-2-carboxamide.